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Published in:
The Lancet Respiratory Medicine

DOI:
10.1016/S2213-2600(18)30427-2

Publication date:
2019

The Lancet Respiratory Medicine

DOI:
10.1016/S2213-2600(18)30427-2

Citation for published version (APA):
Haworth, C. S., Bilton, D., Chalmers, J. D., Davis, A. M., Froehlich, J., Gonda, I.,Thompson, B., Wanner, A., O'Donnell, A. E. (2019).
Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials. The Lancet Respiratory Medicine, 7(3), 213-226. https://doi.org/10.1016/S2213-2600(18)30427-2. Published online January 15, 2019.
This online publication has been corrected. The corrected version first appeared at the lancet.com/respiratory on January 25, 2019.

Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials

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Summary

Background In patients with non-cystic fibrosis bronchiectasis, lung infection with *Pseudomonas aeruginosa* is associated with frequent pulmonary exacerbations and admission to hospital for treatment, reduced quality of life, and increased mortality. Although inhaled antibiotics are conditionally recommended for long-term management of non-cystic fibrosis bronchiectasis with frequent exacerbations, there is no approved therapy. We investigated the safety and efficacy of inhaled, liposomal ciprofloxacin (ARD-3150) in two phase 3 trials.

Methods ORBIT-3 and ORBIT-4 were international, randomised, double-blind, placebo-controlled, phase 3 trials run concurrently in similar geographical regions. Eligible patients had non-cystic fibrosis bronchiectasis, had had at least two pulmonary exacerbations treated with antibiotics in the previous 12 months, and had a history of chronic *P aeruginosa* lung infection. Patients were randomly assigned (2:1) to receive either ARD-3150 or placebo. ARD-3150 (3 mL liposome encapsulated ciprofloxacin 135 mg and 3 mL free ciprofloxacin 54 mg) or 6 mL placebo (3 mL dilute empty liposomes mixed with 3 mL of saline) was self-administered once daily for six cycles of 28 days on-treatment/28 days off-treatment, for 48 weeks. We did primary and secondary efficacy, safety, and microbiology analyses on the full analysis population, which comprised all randomised patients who received at least one dose of study drug. ORBIT-3 and ORBIT-4 are registered with ClinicalTrials.gov, numbers NCT01515007 and NCT02104245, respectively.

Findings Between March 31, 2014, and Aug 19, 2015, we screened 514 patients in ORBIT-3 and 533 patients in ORBIT-4. The full analysis populations consisted of 278 patients in ORBIT-3 (183 patients received at least one dose of ARD-3150 and 95 received placebo) and 304 patients in ORBIT-4 (206 patients received at least one dose of ARD-3150 and 98 received placebo). In ORBIT-4, the median time to first pulmonary exacerbation was 230 days in the ARD-3150 group compared with 158 days in the placebo group, a statistically significant difference of 72 days (hazard ratio [HR] 0·72 [95% CI 0·53–0·97], p=0·032). In ORBIT-3, the median time to first pulmonary exacerbation was 214 days in the ARD-3150 group and 136 days in the placebo group, a non-statistically significant difference of 78 days (HR 0·99 [95% CI 0·71–1·38], p=0·97). In a pooled analysis of data from both ORBIT-3 and ORBIT-4, the median time to first pulmonary exacerbation was 222 days in the ARD-3150 group and 157 days in the placebo group, a non-statistically significant difference of 65 days (0·82

[0·65–1·02], p=0·074). The numbers of adverse events and serious adverse events were similar in both groups in ORBIT-3 and ORBIT-4.

Interpretation

In patients with non-cystic fibrosis bronchiectasis and chronic *P aeruginosa* lung infection requiring antibiotic therapy in the preceding year, ARD-3150 led to a significantly longer median time to first pulmonary exacerbation compared with placebo in ORBIT-4, but not in ORBIT-3 or the pooled analysis. Inconsistency between the trials suggests further research is needed into the heterogeneity of non-cystic fibrosis bronchiectasis and optimal outcome measures for inhaled antibiotics.

Funding Aradigm Corporation.

Research in context

Evidence before this study

We did a literature search using PubMed with no start or end date without limitations, and using the search terms “non-cf bronchiectasis”, “noncystic fibrosis bronchiectasis”, “non cystic fibrosis bronchiectasis”, “dry powder”, “liposome”, “ciprofloxacin”, and “bronchiectasis” to assess all clinical studies that evaluated the use of inhaled antibiotics in the treatment of adult patients with non-cystic fibrosis bronchiectasis before a meeting in February, 2011, with the US Food and Drug Administration to discuss the design of the ORBIT phase 3 trials. We limited our search to studies published in English. Although at that time there were no large, well-controlled trials and no approved therapies of inhaled antibiotics in non-cystic fibrosis bronchiectasis, inhaled antibiotics were anticipated to be effective on the basis of trials in cystic fibrosis. With no established outcome measures, the phase 3 trial design was informed by the results of a phase 2, randomised, double-blind, placebo-controlled trial of once-daily, inhaled antibiotic composed of liposome-encapsulated ciprofloxacin and free ciprofloxacin (ARD-3150) in 42 adults with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa*. In this phase 2 study, ARD-3150 significantly reduced *P aeruginosa* sputum density, significantly delayed time to first pulmonary exacerbation in the population adhering to the protocol, and was well tolerated.

Added value of this study

In patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *P aeruginosa* who had at least two pulmonary exacerbations requiring antibiotics in the preceding year, ARD-3150 significantly prolonged the time to first exacerbation in ORBIT-4 but there was no difference in the time to first exacerbation in the identically designed ORBIT-3 or the pooled analysis. ARD-3150 caused a reduction in the frequency of pulmonary exacerbations over a period of 48 weeks, with pooled data from both studies showing clinically meaningful reductions in all exacerbations, exacerbations requiring antibiotic therapy, and severe exacerbations requiring intravenous antibiotic therapy or admission to hospital for treatment. Both phase 3 trials demonstrated substantial antimicrobial activity of once-daily ARD-3150 against *P aeruginosa* in airways with a safety and tolerability profile similar to placebo. The results of ORBIT-3 and ORBIT-4 provide added

value to the existing literature by supporting the use of inhaled antibiotics in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *P aeruginosa* and frequent exacerbations. Both trials were the first to focus on patients with non-cystic fibrosis bronchiectasis with chronic *P aeruginosa* infection, which is known to be associated with higher morbidity and mortality, and lower quality of life.

Implications of all the available evidence

Although there is no inhaled antibiotic approved for non-cystic fibrosis bronchiectasis, such drugs are conditionally recommended with a moderate amount of evidence to support safety and efficacy in the recent European Respiratory Society guidelines for the management of adult bronchiectasis for long-term treatment in patients with non-cystic fibrosis bronchiectasis who have at least three pulmonary exacerbations per year and chronic lung infections with *P aeruginosa*. Our results suggest that patients with frequent pulmonary exacerbations are more likely to benefit from long-term inhaled antibiotic treatment, which has implications for patient selection in clinical practice and for future clinical trials of inhaled antibiotics in non-cystic fibrosis bronchiectasis.

Introduction

Non-cystic fibrosis bronchiectasis is a chronic lung disease characterised by recurrent infection, inflammation, persistent cough, and production of sputum, [1, 2] and its prevalence is increasing worldwide.[3-5]

Bacteria commonly isolated from the sputum of patients with bronchiectasis include *Pseudomonas aeruginosa, Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis,* and non-tuberculous mycobacteria.[2,6] Chronic *P aeruginosa* infection in patients with non-cystic fibrosis bronchiectasis is of particular concern because it is associated with more severe disease, characterised by frequent exacerbations, hospital admissions, reduced quality of life, and increased mortality.[7,8]

Inhaled antibiotics have the potential to produce higher concentrations in the airways and lower systemic concentrations than with intravenous or oral antibiotics, with potentially fewer systemic adverse effects.[2,6,9–11] Several inhaled antibiotics have been approved for the treatment of cystic fibrosis; however, local intolerability

(occurrence of respiratory side-effects, such as coughing or bronchospasm, because of irritation of the respiratory tract by the inhaled medication) and safety issues or inadequate clinical benefits have restricted the availability of such medications for non-cystic fibrosis bronchiectasis,[12,13] and there is no inhaled antibiotic approved for this disease. Nevertheless, inhaled antibiotics are conditionally recommended in the 2017 European Respiratory Society guidelines for the management of acute bronchiectasis for off-label use for long-term treatment in patients with non-cystic fibrosis bronchiectasis who have at least three pulmonary exacerbations per year and chronic lung infections with *P aeruginosa* because of a moderate amount of supportive clinical data.[14]

ARD-3150 is a once-daily inhaled antibiotic composed of liposome-encapsulated ciprofloxacin and free ciprofloxacin. This drug was designed to overcome the potential intolerance issues associated with some inhaled antibiotics in non-cystic fibrosis bronchiectasis,[12,13,15–19] and to maximise the antipseudomonal activity of ciprofloxacin in the airways by providing a high peak concentration from the free ciprofloxacin component, followed by a slower release of liposomal ciprofloxacin in the airways.[20] The use of biocompatible components in the liposomes reduces the potential for local side-effects, thereby limiting airway irritation.[20,21] Thus, the rationale for the development of ARD-3150 was that reduction of the burden of infection with *P aeruginosa*, achieved with a well tolerated, potent antipseudomonal therapy, would delay onset and reduce the number of pulmonary exacerbations. We did two identical phase 3 trials in patients with non-cystic fibrosis bronchiectasis and chronic *P aeruginosa* lung infection to investigate the efficacy and safety of once-daily ARD-3150.

Methods

Study design and patients

ORBIT-3 and ORBIT-4 were international, randomised, double-blind, placebo-controlled, phase 3 trials run concurrently in similar geographical regions. Other than the participating sites (hospitals, private practices, or clinical research units), there were no differences in design or conduct between the two trials. In ORBIT-3, 514 patients were screened from 16 countries (Australia, Canada, Germany, Hungary, Ireland, Israel, Italy, Latvia, Poland, Romania, South Africa, South Korea, Spain, Taiwan, UK, and USA) and 93 sites randomly assigned at least one patient. In ORBIT-4, 533 patients were screened from 16 countries (Australia, Canada,

France, Georgia, Hungary, Israel, Italy, New Zealand, Peru, Poland, Romania, Serbia, South Korea, Spain, UK, and USA) and 88 sites randomly assigned at least one patient. Eligible patients were aged 18 years or older, had non-cystic fibrosis bronchiectasis confirmed by chest CT, had forced expiratory volume in 1 s (FEV_1) of 25% of predicted or higher, had at least two pulmonary exacerbations treated with antibiotics in the preceding 12 months, and had a history of chronic *P aeruginosa* lung infection as documented by *P aeruginosa* culture in a sputum or deep-throat swab or bronchoalveolar lavage or bronchoscopic specimen before the screening visit. A positive sputum or deep-throat swab culture for *P aeruginosa* with at least one isolate non-resistant to ciprofloxacin was required at screening. Exclusion criteria included a pulmonary exacerbation requiring treatment with antibiotics within 28 days of starting study drug, a primary clinician diagnosis of chronic obstructive pulmonary disease (COPD) related to smoking (>10 pack-years smoking history), cystic fibrosis, and active allergic bronchopulmonary aspergillosis, tuberculosis, or non-tuberculous mycobacterial infection requiring treatment. We also excluded patients using oral or inhaled antipseudomonal antibiotics. Stable macrolide use was permitted if treatment was not initiated within the previous 2 months. Complete inclusion and exclusion criteria are listed in the appendix.

The studies were done in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Guideline for Good Clinical Practice, and applicable local regulations. The trial protocols were approved at each site by an ethics committee or institutional review board. Patients provided written informed consent at enrolment.

Randomisation and masking

Patients were randomly assigned (2:1) to receive either ARD-3150 or placebo. Treatment assignment was accomplished by a computer generated random sequence implemented through an interactive web response system. Randomisation was centralised and stratified by sex (male *vs* female), smoking status (smoker *vs* nonsmoker), and number of pulmonary exacerbations treated with antibiotics during the preceding 12 months (2–3 *vs* ≥4). Study investigators, patients, and funder personnel were masked to treatment assignment. Additional randomization details are described in the appendix.

We used central randomisation to protect the overall intended 2:1 allocation of subjects to ARD-3150 and placebo treatment in the double-blind phase of the study. Blocking was not necessary because of the central randomisation. Study drug was supplied in 5 mL vials colour coded with red and blue vial caps to ascertain that each dose was a mixture of the liposomal and nonliposomal components. The placebo ciprofloxacin for inhalation (CFI) formulation (empty liposomes) was similar in appearance to the active CFI formulation, and the free ciprofloxacin for inhalation (FCI) placebo (isotonic saline) formulation was similar in appearance to the active FCI formulation.

Procedures

ARD-3150 (3 mL liposome encapsulated ciprofloxacin 135 mg and 3 mL free ciprofloxacin 54 mg; 6 mL total; Aradigm Corporation; Hayward, CA, USA) or 6 mL placebo (3 mL dilute empty liposomes mixed with 3 mL of saline) was self-administered once daily with a nebuliser (PARI LC Sprint nebuliser; PARItec GmbH; Starnberg, Germany) for six 56 day treatment cycles (each cycle consisting of a 28 day on-treatment period, followed by a 28 day off-treatment period), for 48 weeks. Study visits were done at the beginning and end of each on-treatment period. Assessments at each study visit included signs and symptoms of pulmonary exacerbation, vital signs, concomitant medications, and adverse events. Tests included spirometry (FEV_1 and FEV_1 % predicted, forced vital capacity [FVC] and FVC % predicted; not done at every visit), sputum cultures, quality of life, and productivity. The Quality of Life-Bronchiectasis (QoL-B) is a validated, self-administered questionnaire consisting of 37 items on eight scales. We assessed productivity with a list of four questions, separate from the QoL-B. Additional tests done at 24 and 48 weeks included serial spirometry, diffusing capacity of the lung for carbon monoxide (also done on day 84; at sites that had the necessary equipment), urinalysis, and blood tests (haematology and clinical chemistry). A schedule of key assessments is provided in the appendix.

Compliance with administration of study drug was assessed by counting returned study drugs. Allowed concomitant medications are listed in the appendix. All patients received standard of care in addition to study

medication. Each patient remained on their prescribed standard medications and therapeutic treatment regimens—with limitations specified by the inclusion and exclusion criteria—for the 48 week duration of the double-blind phase, to which ARD-3150 or placebo was added. Oral, inhaled, and intravenous antibiotics (other than anti-pseudomonal antibiotics), and corticosteroids, bronchodilators, mucolytics, inhaled hypertonic saline or inhaled mannitol, chest physiotherapy, and pulmonary rehabilitation, were defined by the protocol as controlled medications and treatments. Patients who completed double-blind treatment could participate in an open-label extension of one treatment cycle with ARD-3150. We monitored sputum densities of *S pneumoniae*, *H influenzae*, *M catarrhalis*, *S aureus*, and *Escherichia coli* and other coliform species at baseline and all other visits.

Outcomes

The primary and key secondary endpoints were related to the occurrence of pulmonary exacerbations (appendix). We defined a pulmonary exacerbation as the concurrent presence of four or more of the following abnormal respiratory signs, symptoms, or laboratory findings:[22] change in sputum production (consistency, colour, volume, or haemoptysis); increased dyspnoea (chest congestion or shortness of breath); increased cough; fever (≥38°C); increased wheezing; exercise tolerance decrease, malaise, fatigue, or lethargy; FEV_1 or FVC decrease of 10% from a previous value; radiographic changes indicative of a new pulmonary process; and changes in chest sounds. We defined pulmonary exacerbations as mild if there was no antibiotic use or macrolide dose increase to resolve the event. Moderate pulmonary exacerbations required treatment with oral or inhaled antibiotics, or an increase in macrolide dose. Severe pulmonary exacerbations required treatment with intravenous antibiotics or hospital admission. We also analysed pulmonary exacerbation endpoints on the basis of British Thoracic Society (BTS) criteria that require sputum changes (appendix), including increases in volume, viscosity or purulence, and haemoptysis.[2] We used a different pulmonary exacerbation classification for this sensitivity analysis because the optimal definition of a pulmonary exacerbation has not been established.

The primary endpoint was time to the first pulmonary exacerbation from the date of randomisation to week 48.

Secondary endpoints were the total number of pulmonary exacerbations, severe pulmonary exacerbations, and moderate or severe pulmonary exacerbations per patient from the date of randomisation up to week 48. In the case of a discrepancy between investigator assessment and protocol-defined criteria of a pulmonary exacerbation or its severity, adjudication was done by a three-member committee that was blinded to the patient's study group assignment. We also did a subgroup analysis of pulmonary exacerbation frequency in patients with two to three or four or more pulmonary exacerbations in the past year. An additional secondary endpoint was the change from baseline (visit 1) to week 48 in the Respiratory Symptoms Domain Scale (RSS) score for the QoL-B.[23]

We also determined the number of patients in each trial initiating intravenous antibiotics to resolve a severe pulmonary exacerbation by week 48. Microbiology endpoints were the change in *P aeruginosa* density in colony forming units (CFU) per g of sputum from baseline to the start of each on-treatment and off-treatment period and the susceptibility of *P aeruginosa* to ciprofloxacin in vitro, with resistance defined as a ciprofloxacin minimum inhibitory concentration (MIC) greater than 4 μg/mL. A complete list of endpoints is provided in the appendix.

Safety assessments included adverse events, spirometry (FVC, FVC % predicted, FEV_1, and FEV_1 % predicted), and carbon monoxide diffusing capacity (DLco) of the lung adjusted for haemoglobin. For full details of safety assessments see appendix.

Statistical analysis

To calculate the sample size estimate for the primary endpoint of the time to first exacerbation, we used preliminary data for the time to first pulmonary exacerbation analyses from the ORBIT-2 phase 2 trial.[10] Assuming an exponential model for each study with 48-week failure of 80% for placebo and 60% for ARD-3150 (ie, equivalent annual failure rates of 82.5% and 62.9%, respectively), a 2:1 randomisation ratio, 10% loss to follow-up and withdrawal, a two-sided 0.05-level test for significance, and a power of 90%, a

sample size of 234 patients per study would provide 149 cases for the primary analysis endpoint.

We assessed time to first pulmonary exacerbation with the Kaplan-Meier method and stratified unweighted log-rank test. We analysed the number of pulmonary exacerbations with stratified negative binomial regression. We assessed quality of life outcomes using mixed model analysis with repeated measures. We analysed the change in CFU per g sputum with the least squares method, and the MIC of ciprofloxacin for *P aeruginosa* isolates at baseline and each post-baseline visit with Fisher's exact test. Full detail of statistical methods is provided in the appendix.

We adjusted all analyses for previous disease severity (the number of pulmonary exacerbations treated with antibiotics in the year before study enrolment [2–3 *vs* ≥4]), sex (male *vs* female), or the inclusion of covariates to control the analyses for these variables, unless otherwise specified (appendix). Although the protocol called for stratification for smoking status, there were only six smokers in both trials combined, therefore this stratum was not used in the analyses, with approval from regulatory authorities.

As specified in the statistical analysis plan and outlined in the appendix, the negative binomial model for the analysis of the number of pulmonary exacerbations assumed that serial exacerbations within an individual were independent events and the hazard ratio (HR) was uniform as a specified value for the individual. However, more recent information has shown that occurrence of exacerbations increases after previous exacerbations, indicating that pulmonary exacerbation occurrences within an individual are not independent events.[24] Therefore, we did post-hoc analyses using the counting process method[25] to estimate the frequency of pulmonary exacerbations per patient and the effect of potential confounders on the results. This statistical test provides a more robust estimation method when the exact shape of the hazard function is unknown. Additionally, we did a post hoc analysis of the time to subsequent pulmonary exacerbations (ie, after each pulmonary exacerbation) using serial Kaplan-Meier analyses.

We did primary and secondary efficacy, safety, and microbiology analyses on the full analysis population, which comprised all randomised patients who received at least one dose of study drug or placebo. The per-protocol population included patients in the full analysis population who had no major protocol deviations. All calculations were done with SAS version 9.4 or later.

An independent data and safety monitoring board did periodic safety reviews (prespecified based on time and number of subjects, eg, the first prespecified meeting was after 12-week data were available from the first 90 patients from both trials) and one masked analysis (placebo plus ARD-3150 patients pooled together) for the number of first pulmonary exacerbations to assess the validity of sample size assumptions for the primary endpoint.

ORBIT-3 and ORBIT-4 are registered with ClinicalTrials.gov, numbers NCT01515007 and NCT02104245, respectively.

Role of the funding source

The funder of the studies had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 31, 2014, and Aug 19, 2015, we screened 514 patients in ORBIT-3 and 533 patients in ORBIT-4 (appendix; figure 1). The full analysis populations consisted of 278 patients in ORBIT-3 (183 patients received ARD-3150 and 95 received placebo) and 304 patients in ORBIT-4 (206 patients received ARD- 3150 and 98 received placebo). The number of patients achieving a 90% or higher compliance rate was similar in both studies, with 147 (80%) of 183 patients receiving ARD-3150 and 81 (85%) of 95 patients receiving placebo in ORBIT-3 and 179 (87%) of 206 patients receiving ARD-3150 and 83 (85%) of 98 patients receiving placebo in ORBIT-4. The number of patients completing the double-blind treatment period was similar, with

142 (78%) of 183 patients receiving ARD-3150 in ORBIT-3 and 178 (86%) of 206 patients receiving ARD-3150 in ORBIT-4.

Demographics and disease characteristics at study entry were generally well balanced between treatment groups and across the two trials (table 1). Both trials had a higher proportion of patients on ARD-3150 receiving chronic, stable doses of macrolides throughout the trial than patients on placebo. The most prevalent comorbidities present in more than 15% of patients were hypertension, gastro-oesophageal reflux, asthma, and COPD.

Treatment with ARD-3150 resulted in a significant prolongation of median time to first pulmonary exacerbation in ORBIT-4 of 230 days compared with 158 days in the placebo group, a difference of 72 days (treatment effect HR 0.72 [95% CI 0.53–0.97], p=0.032; figure 2; table 2; appendix). Although the median time to first pulmonary exacerbation was 78 days longer in the ARD-3150 group in ORBIT-3 and 65 days longer in the pooled analysis, the differences were not statistically significant (ORBIT-3 HR 0.99 [95% CI 0.71–1.38], p=0.97; pooled HR 0.82 [0.65–1.02], p=0.074; figure 2). Kaplan- Meier plots of the time to first pulmonary exacerbation by week 48 for ORBIT-3, ORBIT-4, and the pooled analysis are shown in figure 2. In ORBIT-4, we observed an early separation of the ARD-3150 and placebo event curves, which was sustained. In ORBIT-3, we found a notable delay in the initial separation of the curves, and the placebo group showed a lower number of pulmonary exacerbations in the second half of the trial, resulting in a convergence of the curves at the end of the trial. This factor explains why, despite the similar difference in the median times between ARD-3150 and placebo in ORBIT-3 and ORBIT-4, the HR in ORBIT-3 was high with broad CIs. In the pooled trials, we found an early separation of the ARD-3150 and placebo event curves, which was sustained.

ARD-3150 treatment was associated with a reduction in the frequency of pulmonary exacerbations of all severity compared with placebo in ORBIT-4, but not in ORBIT-3 (figure 3). In ORBIT-3, the mean number of pulmonary exacerbations per patient assigned to ARD-3150 was 1.09, compared with 1.31 per patient in patients assigned to placebo. The relative risk (RR) for ARD-3150 treatment was 0.85 (95% CI 0.65–1.12;

p=0.26). In ORBIT-4, patients assigned to ARD-3150 had a mean number of pulmonary exacerbations of 0.98 per patient compared with 1.47 per patient in patients assigned to placebo. The RR for ARD-3150 treatment was 0.63 (0.48–0.82; p=0.0006). In the pooled analysis, the mean number of pulmonary exacerbations per patient assigned to ARD-3150 was 1.03, compared with1.39 per patient in patients assigned to placebo, which was also significantly different (RR 0.73 [95% CI 0.60–0.88]; p=0.0011).

In ORBIT-3, the risk reduction in the frequency of severe pulmonary exacerbations with ARD-3150 was not significant (RR 0.80 [95% CI 0.42–1.51]; p=0.48). However, ARD-3150 significantly reduced the frequency of severe pulmonary exacerbations in ORBIT-4 (0.40 [0.22–0.74]; p=0.0031) and the pooled analysis (0.58 [0.37–0.89]; p=0.014; figure 3). In ORBIT-3, the risk for moderate to severe pulmonary exacerbation was not significantly reduced by ARD-3150 compared with placebo (RR 0.78 [95% CI 0.58–1.05]; p=0.10). The frequency of moderate and severe pulmonary exacerbations was significantly reduced with ARD-3150 compared with placebo in ORBIT-4 (0.58 [0.44–0.77]; p=0.0001) and the pooled analysis (0.67 [0.55–0.82]; p=0.0001; figure 3).

We did a subgroup analysis to determine whether the efficacy of ARD-3150 versus placebo was influenced by the historical frequency of pulmonary exacerbations treated with antibiotics in the year before study entry (2–3 or ≥4 pulmonary exacerbations). In ORBIT-3, patients with at least four pulmonary exacerbations in the past year had a greater reduction in pulmonary exacerbation frequency when treated with ARD-3150 versus placebo (RR 0.68 [95% CI 0.44–1.04]) compared with those with two or three pulmonary exacerbations in the past year (0.94 [0.66–1.32]), although these reductions were not significant. In ORBIT-4, patients with at least four pulmonary exacerbations in the past year also had a greater reduction in pulmonary exacerbation frequency when treated with ARD-3150 versus placebo (0.52 [0.31–0.87]) compared with patients with two or three pulmonary exacerbations in the past year (0.68 [0.50–0.93]). We also observed this effect in the pooled analysis, with a greater reduction in pulmonary exacerbation frequency in patients with at least four pulmonary exacerbations in the past year (0.60 [0.43–0.84]) compared with those with two or three pulmonary exacerbations in the past year (0.79 [0.63–0.99]). Pulmonary exacerbation endpoints

analysed using the BTS criteria provided results similar to the primary analysis (appendix).

At baseline, both treatment groups in ORBIT-3 had similar mean QoL-B RSS scores (54.17 for ARD-3150 and 53.59 for placebo). At week 48, the mean QoL-B RSS scores were 58.42 for ARD-3150 and 60.01 for placebo, and we found no significant change from baseline to week 48 between the groups (p=0.45). In ORBIT-4, the ARD-3150 and placebo groups also had similar mean QoL-B RSS scores at baseline (57.72 for ARD-3150 and 56.89 for placebo) and at week 48 (65.46 for ARD-3150 and 65.09 for placebo; p=0.71).

We found no difference between the two treatment groups in the number of patients treated with intravenous antibiotics to resolve a severe pulmonary exacerbation in ORBIT-3 (ARD-3150, 29 [16%] of 184 patients and placebo, 13 [14%] of 95 patients; p=0.63), whereas the difference was significant in ORBIT-4 (ARD-3150 23 [11%] of 205 patients, and placebo 22 [22%] of 98 patients; p=0・01). We found no difference in the pooled analysis (ARD-3150, 44 [11%] of 389 patients and placebo, 32 [17%] of 193 patients) for ARD-3150 versus placebo.

ARD-3150 significantly reduced the sputum density of *P aeruginosa* compared with placebo on day 28 of the first dosing period by –1.87 $\log_{10}$ CFU per g (least squares mean; SE 0.38) in ORBIT-3 and –1.80 $\log_{10}$ CFU per g (0.37) in ORBIT-4 (p<0.0001 for both). Except for one visit (week 20, visit 7; third treatment cycle) in ORBIT-3, we observed consistent significant reductions from baseline in least squares mean $\log_{10}$ CFU per g of sputum at the end of every on-treatment period throughout the course of both studies (figure 4). The CFU count was similar to the baseline measurement at the end of the off-treatment periods.

At baseline, 100 (21%) of 487 *P aeruginosa* isolates had a MIC of 4 μg/mL or greater. MIC tended to increase on treatment with ARD-3150 and decrease towards baseline during off-treatment periods (appendix). After 48 weeks, 62 (32%) of 191 patients treated with ARD-3150 and 17 (18%) of 97 patients treated with placebo had a *P aeruginosa* isolate for which the ciprofloxacin MIC had increased by more than two times (p=0.0078).

The numbers of adverse events and serious adverse events were similar in both treatment groups in ORBIT-3 and ORBIT-4 (table 3). In the pooled analysis, 21 (5%) of 389 patients assigned to ARD-3150 and seven (4%) of 196 patients assigned to placebo withdrew because of an adverse event (figure 1). The only adverse event leading to withdrawal for 1% or more of patients was dyspnea (four [1%] of 389 patients in the ARD-3150 group and two [1%] of 193 patients in the placebo group). The most common adverse events related to airway irritation were cough, dyspnoea, wheezing, and oropharyngeal pain, with no difference in occurrences between patients assigned to ARD-3150 and patients assigned to placebo (table 3). Most adverse events were mild or moderate. Reports of bronchospasm were low and similar in both groups (1% in the ARD-3150 group and 1% in the placebo group in the pooled analysis). We found no evidence of an increased frequency in any of the common quinolone class effects with ARD-3150 versus placebo (table 4). No new safety signals were observed in the open-label extension phase of the studies.

We found no significant difference between the treatment groups for spirometry results (FEV_1, FEV_1 % predicted, FVC, and FVC % predicted) over the 48 week trial period (appendix). Likewise, we found no difference between the ARD-3150 and placebo groups for the number of patients whose serial post-dose FEV_1 predicted percentage decreased by 15% or more at the 15 min, 30 min, and 90 min post-dose timepoints relative to the pre-dose value at either visit 1 or visit 8 (data not shown). Additionally, we found no difference between groups in the mean change from baseline in haemoglobin-adjusted diffusing capacity of the lungs for carbon monoxide at 48 weeks (data not shown).

By use of the counting process method, we investigated the effect of major protocol deviations on pulmonary exacerbation frequency in the per-protocol population as another possible explanation for the differences in results between ORBIT-3 and ORBIT-4. The most common protocol deviation was use of antibacterial therapies for reasons other than a protocol-defined pulmonary exacerbation, and these were more prevalent in patients assigned to placebo. Generally, in ORBIT-3 and the pooled analysis, ARD-3150 showed a more favourable reduction of all pulmonary exacerbations, severe pulmonary exacerbations, and moderate and severe pulmonary exacerbations in the per-protocol compared with the full analysis population, as shown by

lower RR values, whereas there was very little difference between the analyses in the per-protocol and full analysis populations in ORBIT-4 (appendix).

We did post-hoc serial Kaplan-Meier log-rank analyses of time to subsequent pulmonary exacerbations in ORBIT-3 and ORBIT-4 in the full analysis population (table 5, appendix). In ORBIT-3, a trend ($p_{trend}<0.1$) for extended pulmonary exacerbation-free intervals in ARD-3150 compared with placebo was observed from the third serial pulmonary exacerbation onwards. In ORBIT-4, the differences between treatment groups were more pronounced, with significant ($p<0.05$; table 5) differences between ARD-3150 and placebo observed for most serial pulmonary exacerbation events, beginning with the first serial pulmonary exacerbation.

Post-hoc analysis of the full analysis population indicated that patients with chronic macrolide use at baseline generally had a higher frequency of pulmonary exacerbations during the trials than did patients without chronic macrolide use, suggesting higher disease activity (appendix). Stratification for chronic macrolide use in ORBIT-3 reduced the RR for pulmonary exacerbation frequency in the ARD-3150 groups compared with the placebo group in all pulmonary exacerbation categories (appendix).

Sensitivity testing of *P aeruginosa* isolates to other antimicrobials (amikacin, aztreonam, cefepime, ceftazidime, gentamicin, meropenem, piperacillin, ticarcillin plus clavulanic acid, and tobramycin) indicated that only the proportion of isolates having a greater than two times increase in MIC for aztreonam over the 48 week treatment period were different ($p=0.037$) between ARD-3150 (32 [17%] of 191 patients) and placebo (21 [22%] of 97 patients). We did a post-hoc proportional hazards analysis to investigate the RR of a pulmonary exacerbation among subgroups of patients on the basis of *P aeruginosa* MIC. A higher ciprofloxacin MIC (≥4 μg/mL) at baseline or at any time during the 48 week trial period was not associated with a greater risk of a pulmonary exacerbation (appendix).

Discussion

We observed that once-daily ARD-3150 (liposomal ciprofloxacin) treatment caused a statistically significant

and clinically meaningful improvement in the time to first pulmonary exacerbation in ORBIT-4, a result that was not replicated in ORBIT-3 or the pooled analysis. ARD-3150 showed meaningful efficacy for reduction of pulmonary exacerbations for 12 months in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *P aeruginosa* and at least two antibiotic-treated pulmonary exacerbations in the past year. The pooled data from ORBIT-3 and ORBIT-4 showed a risk reduction in all pulmonary exacerbations and severe pulmonary exacerbations, differences that are clinically relevant in a population of patients with a high burden of disease.

ARD-3150 significantly prolonged the median time to first pulmonary exacerbation—the primary endpoint—in ORBIT-4, but not in ORBIT-3 or the pooled analysis. Although time to first pulmonary exacerbation has been used as a surrogate estimate of reduction in the number of pulmonary exacerbations, the inconsistent results presented here suggest that time to first pulmonary exacerbation might not be a reliable outcome measure by which to estimate the effectiveness of therapy, especially within the setting of a chronic disease with the potential for frequent pulmonary exacerbations. In clinical practice, the primary goal of treatment is to reduce the number of pulmonary exacerbations, particularly severe pulmonary exacerbations,[14,26] because patients with the highest proportion have the greatest risk of future mortality, a decreased quality of life, and a greater future risk of such events.[26] Importantly, the strongest predictor of a future pulmonary exacerbation is a previous history of pulmonary exacerbations.[24]

We found that the QoL-B RSS did not improve after 48 weeks. QoL-B has a 7 day recall period; therefore, this method of analysis does not consider potential differences in respiratory symptoms that patients might have had during the course of the full 48 week trial. Further investigations of the effect of inhaled antibiotics on quality of life are needed.

Reduced frequency of pulmonary exacerbations with ARD-3150 in patients with non-cystic fibrosis bronchiectasis who are chronically infected with *P aeruginosa* might be related to a reduction of bacterial load and improvement in airway inflammation.[27,28] We showed the antimicrobial activity of ciprofloxacin against *P*

aeruginosa in the lung by the significant reduction in sputum density of this pathogen with ARD-3150 treatment compared with placebo treatment during on-treatment periods. We observed no attenuation of this effect during the 48 week trials.

A concern with long-term treatment with inhaled antibiotics is the development of antibiotic resistance. Although the distribution of ciprofloxacin MICs among *P aeruginosa* isolates shifted to somewhat higher MICs after the first on-treatment period with ARD-3150, MICs tended to decrease by the end of the off-treatment periods. Interpretive criteria for bacterial susceptibility are based on achievable serum concentrations from systemic administration of ciprofloxacin. Susceptibility criteria based on MIC probably do not predict clinical outcomes because of the substantially increased ciprofloxacin concentrations in the lungs with inhalation of ARD-3150 compared with concentrations achievable by oral or intravenous administration.[20] A post-hoc analysis found that there was no attenuation of the beneficial effect of ARD-3150 on the relative risk of a pulmonary exacerbation in patients who had ciprofloxacin MICs of 4 µg/mL or greater, either at baseline or that developed during the trials (appendix).

In both ORBIT-3 and ORBIT-4, ARD-3150 was well tolerated, with a safety and tolerability profile similar to placebo. Use of ARD-3150 for 48 weeks did not cause reduction of lung function measured by FEV1 or FVC and haemoglobin-adjusted DLco compared with placebo. The risk of bronchospasm with ARD-3150 was low.[29] The tolerability of ARD-3150 was also evidenced by the high amount of compliance seen in both trials.

We found no evidence of an increased frequency of any of the known adverse effects associated with the quinolone class of drugs[30] in patients receiving ARD-3150. These findings were consistent with the low systemic exposure to ciprofloxacin that has been observed after inhaled ARD-3150.[20]

With many unanswered questions remaining regarding patients with non-cystic fibrosis bronchiectasis who could benefit from long-term inhaled antibiotic therapy, we did additional post-hoc analyses with the aim of investigating possible reasons for the disparate results between ORBIT-3 and ORBIT-4. Since the

commencement of the ORBIT phase 3 trials, information has been evolving regarding recognition of the frequent exacerbator phenotype.[14,24] Patients with high rates of pulmonary exacerbation (≥3 per year) have more severe disease, a high risk of hospital admissions, poor quality of life, and an increased risk of death.[24] In the ORBIT trials, we stratified patients by the frequency of pulmonary exacerbations in the previous year (≥4 or 2–3), which allowed us to examine the effect of ARD-3150 in pre-specified frequent exacerbators. This subgroup analysis suggested that frequent exacerbators are likely to benefit most from inhaled ARD-3150, which is in line with the new European Respiratory Society guidelines on the management of adult bronchiectasis, in which long-term inhaled antibiotic therapy is conditionally recommended in patients with frequent exacerbations.[14]

Recognition that patients with frequent pulmonary exacerbations are more likely to benefit from long-term inhaled antibiotic treatment suggests that only evaluating the time to the first pulmonary exacerbation might not reveal the benefit of therapy in patients with frequent exacerbations. Our exploratory post-hoc analysis of the time to first and subsequent pulmonary exacerbations provided additional insight. In ORBIT-3, the results favoured ARD-3150 after the third pulmonary exacerbation, suggesting benefit in patients with a higher burden of disease that would not be apparent if only recording the first such event.

We do not fully understand the underlying reasons for the differences in the results between ORBIT-3 and ORBIT-4. An additional post-hoc analysis of pulmonary exacerbation frequency by use of the counting process method[25] allowed for stratification for macrolide use at baseline and for assessment of the effect of major protocol deviations on cumulative pulmonary exacerbation events. Considering these factors generally resulted in improved RRs and narrower CIs, thus strengthening the observed positive effect of ARD-3150 on the reduction of pulmonary exacerbations. The use of a statistical model that accounts for interdependence between pulmonary exacerbations, corrects for major protocol deviations, and adjusts for the imbalance in macrolide use at baseline, appears to explain to some extent the apparent differences between the effect of ARD-3150 treatment on pulmonary exacerbations in ORBIT-3 compared with ORBIT-4.

Macrolide use has increased substantially in some countries over the past 5 years following the publication of several trials showing their beneficial effects on exacerbations in non-cystic fibrosis bronchiectasis.[31–33] The decision not to stratify for baseline macrolides in the ORBIT trials was made before the publication of these studies and was, in retrospect, a limitation. The observed imbalance in the use of chronic macrolides between the placebo and ARD-3150 groups at study enrolment could have affected the results. A limitation of the present study was the lower than expected number of pulmonary exacerbations during the double-blind period in patients in the placebo groups, which was less than the at least two pulmonary exacerbations per year specified in the inclusion criteria. The reason for the lower number of pulmonary exacerbations is unclear, but this is consistent with what has been reported in previous bronchiectasis clinical trials and is a recognised phenomenon in trials of other conditions.[34,35] Patients with a higher number of pulmonary exacerbations in the previous year at study entry had a more robust response to treatment than did those with a lower number of pulmonary exacerbations in the previous year.

An additional limitation of this study was that although the post-hoc tests supported the overall effect of ARD-3150 in reducing pulmonary exacerbation frequency, these analyses can only be considered hypothesis-generating and should be interpreted with caution.

Use of inhaled antibiotics to manage chronic respiratory infections in non-cystic fibrosis bronchiectasis is attractive to maximise local efficacy and minimise systemic side-effects. However, the absence of universally accepted endpoints has been a major obstacle in the development of inhaled antibiotics for non-cystic fibrosis bronchiectasis, and conclusive evidence of a positive benefit–risk ratio for inhaled antibiotics in non-cystic fibrosis bronchiectasis has been elusive.[26,36,37] Several large randomised controlled trials of inhaled antibiotics have been done in non-cystic fibrosis bronchiectasis. The development of some compounds has been restricted by the adverse effect of bronchospasm, particularly for aminoglycosides.[13,17] By contrast, ARD-3150 showed no increased risk of bronchospasm compared with placebo. Studies with inhaled colistin,[16] dry powder ciprofloxacin[34,38] and aztreonam[15] did not reach their primary endpoints, but were done in different patient

populations to ours and used very different study designs. The present study is the only large-scale 12 month study in a population of patients with chronic *P aeruginosa* infection.

In patients with non-cystic fibrosis bronchiectasis who have chronic lung infection with *P aeruginosa* and previous pulmonary exacerbations requiring antibiotics, ARD-3150 significantly reduced the mean time to first pulmonary exacerbation in ORBIT-4, but not in ORBIT-3 or the pooled analysis. Overall, ARD-3150 reduced pulmonary exacerbations, and the adverse event profile was similar to placebo. The results of ORBIT-3 and ORBIT-4 suggest that ARD-3150 might provide benefit to patients with non-cystic fibrosis bronchiectasis with frequent pulmonary exacerbations.

Contributors

Aradigm Corporation, the study funder, designed the protocol in consultation with AEO'D and DB. All authors were involved in interpretation of the data and contributed to the manuscript. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CSH reports personal fees from Aradigm Corporation and Grifols, during the conduct of the study; and personal fees from Chiesi, Gilead, GlaxoSmithKline, and Zambon; and personal fees and grants from Insmed, Teva, and Vertex, outside of the submitted work. DB reports personal fees from Aradigm Corporation during the conduct of the study. JDC reports personal fees from Aradigm Corporation and Napp; grants from AstraZeneca; and personal fees and grants from Bayer Healthcare, Boehringer-Ingelheim, GlaxoSmithKline, Grifols, Insmed, and Pfizer, all outside of the submitted work. AMD reports employment with Grifols during the conduct of the study. JF reports employment with Aradigm Corporation during the conduct of the study. IG reports employment with Aradigm Corporation during the conduct of the study; and consultancy with Aradigm Corporation, outside of the submitted work. BT reports consultancy with Aradigm Corporation during the conduct of the study. AW reports personal fees with Aradigm Corporation during the conduct of the study. AEO'D reports grants from Aradigm Corporation during the conduct of the study; and personal fees

and grants from Bayer, consultancy and grants from Insmed, grants from COPD Foundation/US Bronchiectasis Registry, and personal fees from Grifols and Horizon, all outside of the submitted work.

Data sharing

Data reported in this manuscript are available within the Article and its supplementary materials. Additional data from ORBIT-3 (ARD-3150-1201; NCT01515007) and ORBIT-4 (ARD-3150-1202; NCT02104245) can be requested at ARD3150ClinicalTrial@aradigm.com.

Acknowledgments

We thank the patients and their families, and the multinational team of clinicians and investigators who participated in these trials. These trials were funded by Aradigm Corporation. Medical writing and editorial assistance were provided by Alex Loeb and Susan Sutch of Evidence Scientific Solutions (Philadelphia, PA, USA), which were funded by Grifols. Primary results of the ORBIT studies have been presented in abstract form at the American Thoracic Society International Conference (May 19–24, 2017; Washington, DC, USA); the International Society for Aerosols in Medicine (June 3-7, 2017; Sante Fe, NM, USA); and the 2nd World Bronchiectasis Conference (July 6–8, 2017; Milan, Italy). The affiliation for IG was correct at the time of the study, but IG is currently an independent consultant.

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Table 1: **Patient demographics and baseline characteristics**

	ORBIT-3		ORBIT-4		Pooled	
	ARD-3150 (n=183)	**Placebo (n=95)**	**ARD-3150 (n=206)**	**Placebo (n=98)**	**ARD-3150 (n=389)**	**Placebo (n=193)**
Age (years)	64·3(13·6)	66·7(10·7)	63·3(13·5)	64·2(12·6)	63·8(13·5)	65·5(11 7)
Sex						
Female	127 (69%)	67 (71%)	134 (65%)	63 (64%)	261 (67%)	130 (67%)
Male	56 (31%)	28 (29%)	72 (35%)	35 (36%)	128 (33%)	63 (33%)
Race						
White	161 (88%)	89 (94%)	168 (82%)	82 (84%)	329 (85%)	171 (89%)
Asian	15 (8%)	4 (4%)	11 (5%)	4 (4%)	26 (7%)	8 (4%)
Black	3 (2%)	1 (1%)	2 (1%)	1 (1%)	5 (1%)	2 (1%)
Other*	4 (2%)	1 (1%)	25 (12%)	11 (11%)	29 (7%)	12 (6%)
Ethnicity Hispanic or Latino	6 (3%)	3 (3%)	25 (12%)	9 (9%)	31 (8%)	12 (6%)
Baseline forced expiratory volume in 1 s (% predicted)	57·3(21·9)	57·4(20·2)	62·6(22·2)	59·8(20·8)	60·1(22·2)	58·6(20·5)
Number of pulmonary exacerbations treated with antibiotics in the 12 months before screening†						
2–3	141 (77%)	69 (73%)	166 (81%)	76 (78%)	307 (79%)	147 (76%)
≥4	42 (23%)	25 (26%)	40 (19%)	21 (21%)	82 (21%)	46 (24%)
Macrolide use	43 (23%)	13 (14%)	34 (17%)	24 (24%)	77 (20%)	37 (19%)
Current smokers	3 (2%)	1 (1%)	2 (1%)	0	5 (1%)	1 (1%)
Non-Pseudomonas pathogens						
Staphylococcus. aureus	31 (17%)	22 (23%)	50 (24%)	23 (23%)	81 (21%)	45 (23%)
Escherichia coli and other coliform species	11 (6%)	5 (5%)	9 (4%)	3 (3%)	20 (5%)	8 (4%)
Streptococcus. pneumoniae	5 (3%)	3 (3%)	10 (5%)	3 (3%)	15 (4%)	6 (3%)
Haemophilus influenzae	5 (3%)	1 (1%)	7 (3%)	4 (4%)	12 (3%)	5 (3%)
Moraxella. catarrhalis	2 (1%)	0	0	0	2 (1%)	0
Comorbidities in ≥10% of patients in at least one patient group‡						
Asthma	40 (21%)	27 (28%)	41 (20%)	21 (21%)	81 (21%)	48 (25%)
Chronic obstructive pulmonary disease	39 (20%)	15 (15%)	36 (17%)	17 (17%)	75 (19%)	32 (17%)

	ORBIT-3		ORBIT-4		Pooled	
	ARD-3150 (n=183)	**Placebo (n=95)**	**ARD-3150 (n=206)**	**Placebo (n=98)**	**ARD-3150 (n=389)**	**Placebo (n=193)**
Chronic sinusitis	23 (12%)	7 (7%)	15 (7%)	5 (5%)	38 (10%)	12 (6%)
Depression	35 (18%)	21 (22%)	16 (8%)	10 (10%)	51 (13%)	31 (16%)
Gastro-oesophageal reflux disease	54 (28%)	34 (35%)	41 (20%)	19 (19%)	95 (24%)	53 (27%)
Hypertension	62 (32%)	40 (41%)	83 (40%)	35 (35%)	145 (37%)	75 (39%)
Hypercholesterolaemia	20 (10%)	13 (13%)	17 (8%)	10 (10%)	37 (9%)	23 (12%)
Hypothyroidism	25 (13%)	14 (14%)	15 (7%)	6 (6%)	40 (10%)	20 (10%)
Osteoporosis	30 (16%)	18 (19%)	23 (11%)	17 (17%)	53 (14%)	35 (18%)
Osteoarthritis	24 (12%)	23 (24%)	26 (13%)	14 (14%)	50 (13%)	37 (19%)
Sinusitis	16 (8%)	8 (8%)	17 (8%)	12 (12%)	33 (8%)	20 (10%)

Data are mean (SD) or n (%). *Includes categories of American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiracial, or not reported. †Two patients (one in each study) included in the 2–3 pulmonary exacerbations category were randomly assigned as having two previous pulmonary exacerbations, but were later determined to have only one such previous event. ‡Percentages are calculated from the intent-to-treat population (ORBIT-3: ARD-3150 193 patients, placebo 97 patients; ORBIT-4: ARD-3150 207 patients; placebo 101 patients; pooled analysis: ARD-3150 400 patients; placebo 198 patients).

Table 2: **Time in days to first pulmonary exacerbation by week 48, stratified by sex and previous pulmonary exacerbations**

	ARD-3150	Placebo
ORBIT-3	214 (114-289)	136 (81-339)
ORBIT-4	230 (187-NA)	158 (79-238)
Pooled analysis	222 (178-271)	157 (89-238)

Data are median (95% CI). NA=not applicable.

Table 3: Adverse events during the double-blind period of ORBIT-3 and ORBIT-4

	ORBIT-3		ORBIT-4		Pooled	
	ARD-3150 (n=183)	Placebo (n=95)	ARD-3150 (n=206)	Placebo (n=98)	ARD-3150 (n=389)	Placebo (n=193)
Patients with an adverse event	164 (90%)	87 (92%)	179 (87%)	95 (97%)	343 (88%)	182 (94%)
Patients with an adverse event related to study drug	78 (43%)	32 (34%)	58 (28%)	35 (36%)	136 (35%)	67 (35%)
Patients with a serious adverse event	56 (31%)	24 (25%)	35 (17%)	28 (29%)	91 (23%)	52 (27%)
Patients with a serious adverse event related to study drug	6 (3%)	1 (1%)	1 (<1%)	1 (1%)	7 (2%)	2 (1%)
Deaths*	5 (3%)	3 (3%)	1 (<1%)	2 (2%)	6 (2%)	5 (3%)
Adverse event in ≥5% of patients						
Cough	114 (62%)	55 (58%)	137 (67%)	71 (72%)	251 (65%)	126 (65%)
Dyspnoea	104 (57%)	48 (51%)	107 (52%)	55 (56%)	211 (54%)	103 (53%)
Increased sputum	82 (45%)	43 (45%)	99 (48%)	64 (65%)	181 (47%)	108 (56%)
Wheezing	69 (38%)	35 (37%)	84 (41%)	49 (50%)	153 (39%)	84 (43%)
Increased bronchial secretion viscosity	23 (13%)	12 (13%)	43 (21%)	25 (26%)	66 (17%)	37 (19%)
Haemoptysis	31 (17%)	9 (9%)	27 (13%)	18 (18%)	58 (15%)	27 (14%)
Oropharyngeal pain	9 (5%)	7 (7%)	10 (5%)	13 (13%)	19 (5%)	20 (10%)
Rhinorrhoea	3 (2%)	6 (6%)	11 (5%)	9 (9%)	14 (4%)	15 (8%)
Discoloured sputum	8 (4%)	4 (4%)	5 (2%)	7 (7%)	13 (3%)	11 (6%)
Chest pain	12 (7%)	5 (5%)	11 (5%)	4 (4%)	23 (6%)	9 (5%)
Chest discomfort	10 (5%)	3 (3%)	9 (4%)	7 (7%)	19 (5%)	10 (5%)
Fatigue	71 (39%)	40 (42%)	71 (34%)	49 (50%)	142 (37%)	89 (46%)
Decreased exercise tolerance	44 (24%)	22 (23%)	54 (26%)	33 (34%)	98 (25%)	55 (28%)
Pyrexia	48 (26%)	31 (33%)	42 (20%)	25 (26%)	90 (23%)	56 (29%)
Malaise	16 (9%)	15 (16%)	36 (17%)	14 (14%)	52 (13%)	29 (15%)
Decreased FEV_1	62 (34%)	19 (20%)	70 (34%)	33 (34%)	132 (34%)	52 (27%)
Abnormal breath sounds	42 (23%)	17 (18%)	61 (30%)	28 (29%)	103 (26%)	45 (23%)
Decreased FVC	37 (20%)	14 (15%)	48 (23%)	24 (24%)	85 (22%)	38 (20%)
Abnormal sputum	22 (12%)	12 (13%)	24 (12%)	15 (15%)	46 (12%)	27 (14%)
Decreased PFT	19 (10%)	11 (12%)	1 (<1%)	1 (1%)	20 (5%)	12 (6%)
Purulent sputum	34 (19%)	13 (14%)	52 (25%)	37 (38%)	86 (22%)	50 (26%)
Nasopharyngitis	8 (4%)	5 (5%)	13 (6%)	6 (6%)	21 (5%)	11 (6%)
Pneumonia	12 (7%)	7 (7%)	8 (4%)	0	20 (5%)	7 (4%)
Lethargy	39 (21%)	18 (19%)	49 (24%)	20 (20%)	88 (23%)	38 (20%)
Headache	21 (11%)	11 (12%)	23 (11%)	14 (14%)	44 (11%)	25 (13%)
Dysgeusia	19 (10%)	6 (6%)	13 (6%)	7 (7%)	32 (8%)	13 (7%)
Dizziness	15 (8%)	5 (5%)	13 (6%)	4 (4%)	28 (7%)	9 (5%)
Nausea	16 (9%)	4 (4%)	14 (7%)	7 (7%)	30 (8%)	11 (6%)
Diarrhoea	7 (4%)	9 (9%)	14 (7%)	10 (10%)	21 (5%)	19 (10%)
Arthralgia	10 (5%)	4 (4%)	13 (6%)	5 (5%)	23 (6%)	9 (5%)
Back pain	13 (7%)	3 (3%)	8 (4%)	3 (3%)	21 (5%)	6 (3%)
Bronchospasm†	4 (2%)	1 (1%)	1 (<1%)	1 (1%)	5 (1%)	2 (1%)

Data are n (%). FEV1=forced expiratory volume in 1 s. FVC=forced vital capacity. PFT=pulmonary function tests. *No deaths were considered related to study drug. †Adverse event of special interest occurring in <5% of patients.

Table 4: **Side-effects associated with the quinolone class of antibiotics over the 48-week double-blind study period (pooled analysis)**

	ARD-3150 (n=389)	**Placebo (n=193)**
Tendonitis	3 (1%)	1 (1%)
Tendon rupture	0	1 (1%)
Paraesthesia	0	2 (1%)
Muscle weakness	3 (1%)	0
Nervous system disorder	153 (39%)	72 (37%)
Psychiatric disorders	21 (5%)	16 (8%)
Drug hypersensitivity	2 (1%)	0
Hepatobiliary disorder	4 (1%)	3 (2%)
Diarrhoea (any)	21 (5%)	19 (10%)
QTc change >30 ms	21 (5%)	13 (7%)
QTc change >60 ms	8 (2%)	6 (3%)
Photosensitivity	1 (<1%)	0

Data are n (%).

Table 5: **Post-hoc analysis of serial Kaplan-Meier log-rank test**

	Patients with pulmonary exacerbations on ARD-3150	Patients with pulmonary exacerbations on placebo	Log-Rank	Nominal p-value
ORBIT-3				
First event	109	54	0·014	0·91
Second event	55	33	0·68	0·41
Third event	23	19	2·77	0·096
Fourth event	10	14	8·71	0·0032
Fifth event	2	4	2·96	0·086
Sixth event	0	0	–	–
ORBIT-4				
First event	114	64	4·93	0·026
Second event	57	39	8·11	0·0044
Third event	19	23	13·34	0·0003
Fourth event	8	8	2·70	0·10
Fifth event	3	5	3·30	0·069
Sixth event	1	2	1·48	0·22
Seventh event	0	2	3·71	0·054
Eighth event	0	1	1·79	0·18

Figure 1: **Trial profiles**

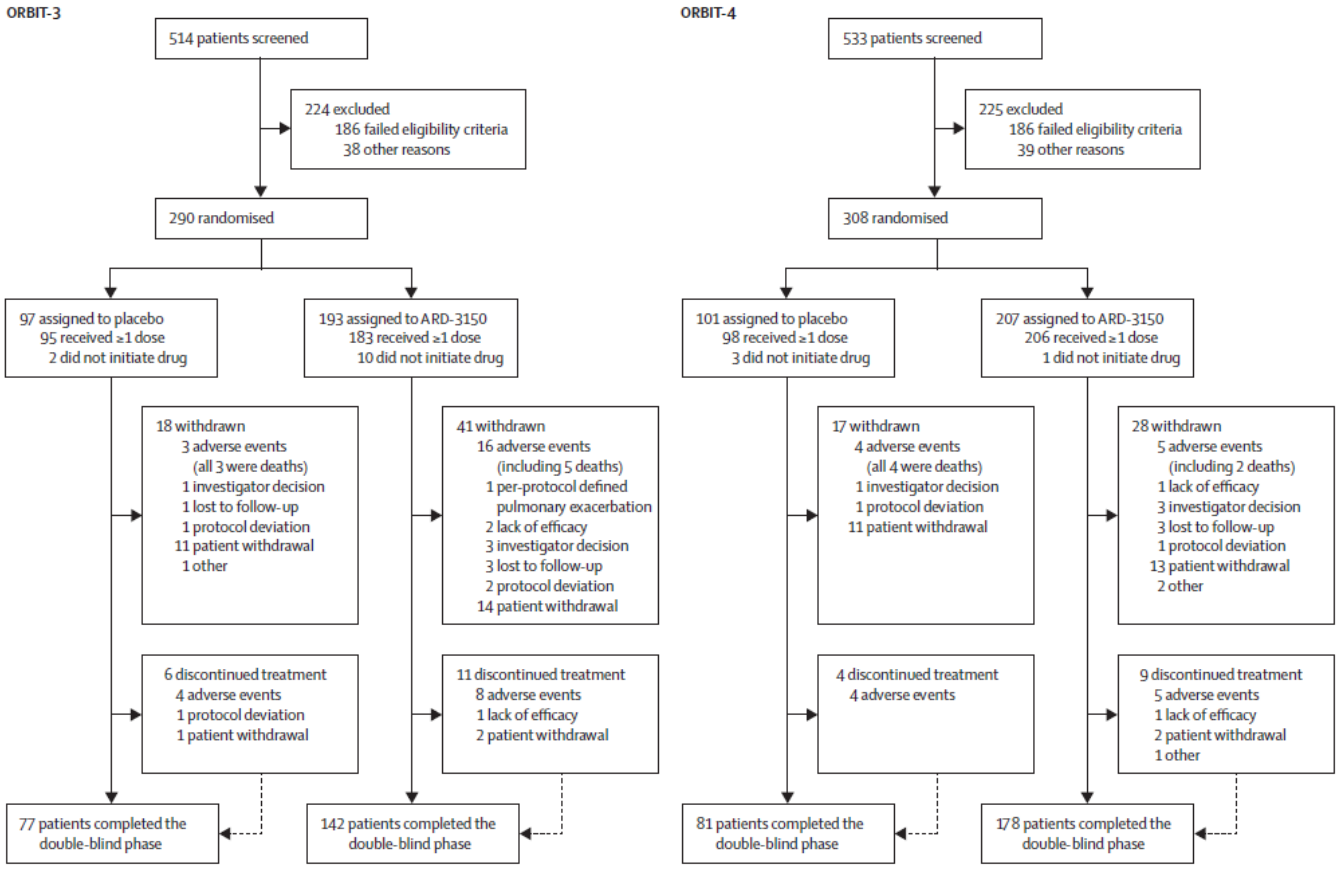
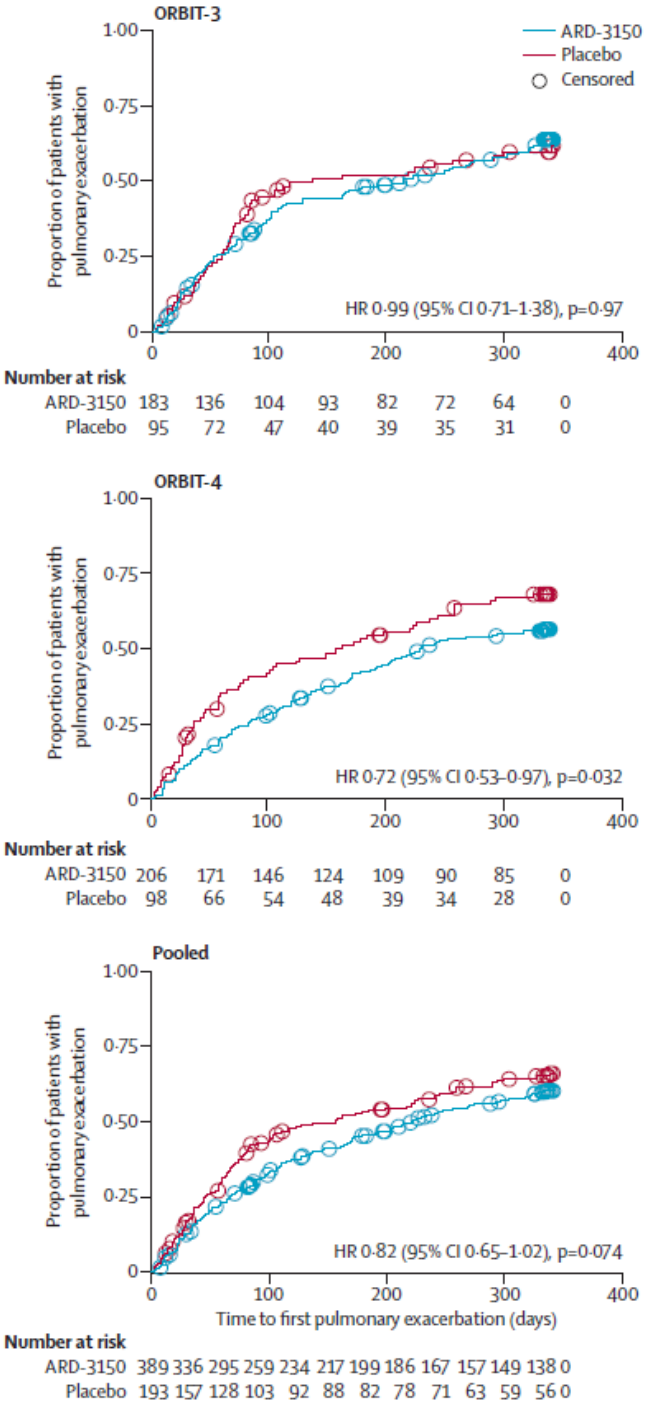
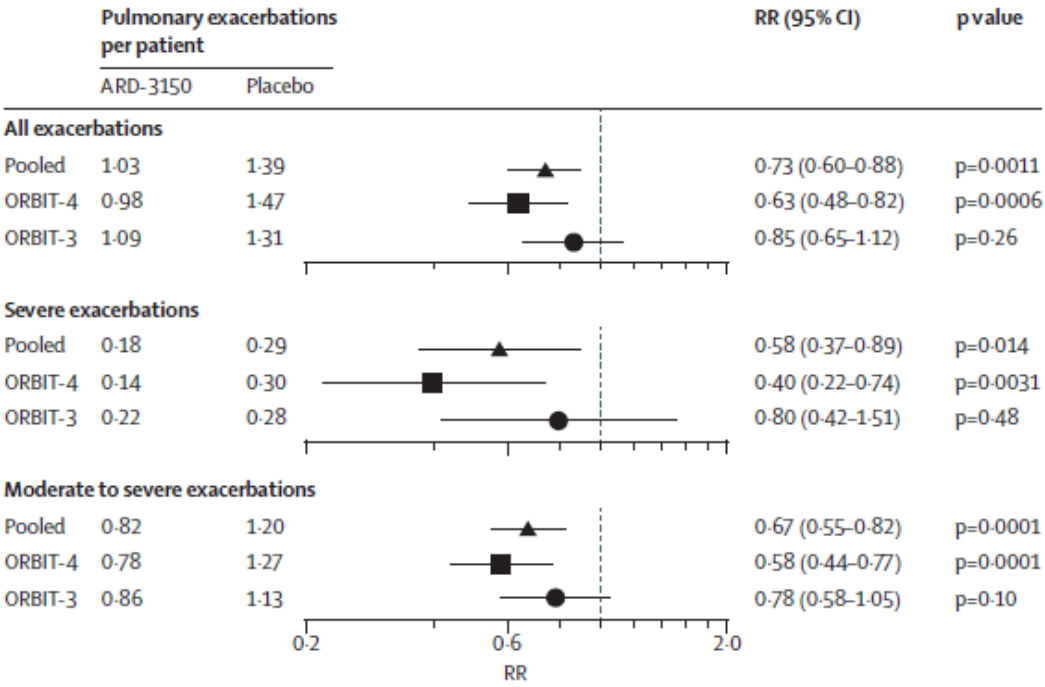


Figure 2: **Time to first pulmonary exacerbation**



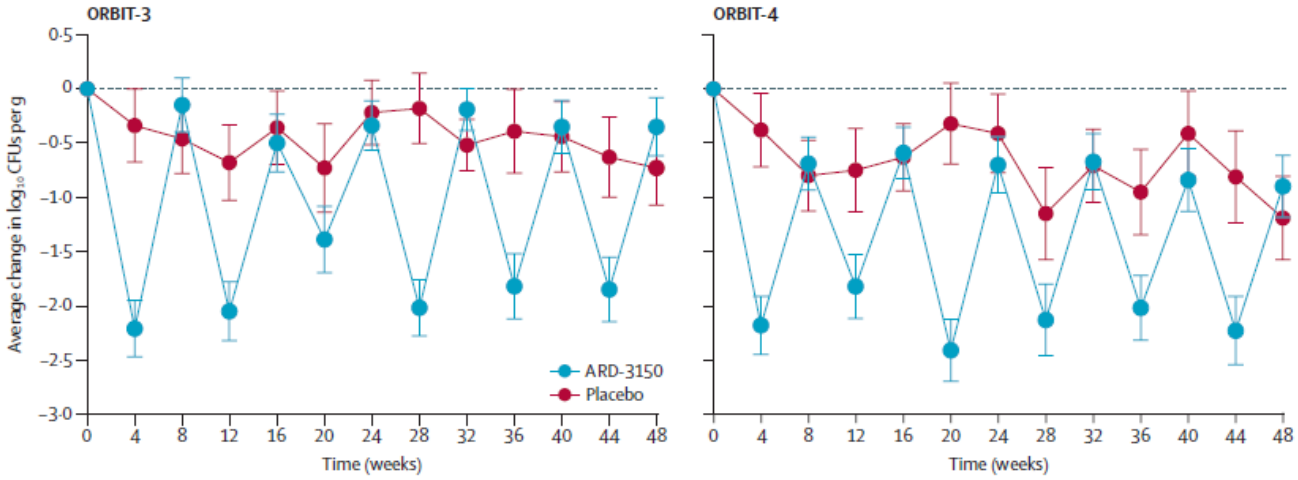
Kaplan-Meier plots of time to first pulmonary exacerbation by week 48 for ORBIT-3, ORBIT-4, and the pooled analysis. HR=hazard ratio.

Figure 3: Exacerbation frequency analysis



Forest plots of all exacerbation frequency, severe exacerbation frequency, and moderate and severe exacerbation frequency. Plots show the number of pulmonary exacerbations per patient from baseline to week 48, analysed by negative binomial regression stratified by sex and number of pulmonary exacerbations in the previous year. Error bars represent 95% CIs. The vertical dotted line represents an RR of 1. RR=relative risk.

Figure 4: **Change in sputum density of *Pseudomonas aeruginosa* over the 48-week double-blind period**



Data are least squares mean. Error bars represent SE. CFU=colony-forming units.